

# Genetic basis of ethnic disparities in VTE risk

Nigel S. Key<sup>1</sup> and Alex P. Reiner<sup>2</sup> <sup>1</sup>UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL; <sup>2</sup>UNIVERSITY OF WASHINGTON

In this issue of *Blood*, Hernandez et al identify and replicate single-nucleotide polymorphisms on chromosome 20 (and putatively on the *THBD* gene for thrombomodulin) that increased the risk of venous thromboembolism (VTE) by about 2.3-fold in African Americans (AAs) in the United States.<sup>1</sup>

**A**s experience higher rates of VTE than their white American counterparts,<sup>2</sup> particularly in the Southeastern United States.<sup>3</sup> The reasons for the higher burden of VTE risk among AAs are complex and likely include a combination of differences in acquired and genetic VTE risk factors, as well as socioeconomic status/health care access. Despite the fact that a positive family history of VTE is elicited as commonly in affected AA patients,<sup>4</sup> the two most prevalent and well-established genetic risk factors for VTE (the factor V Leiden and prothrombin G20210A mutations) are considerably more common among individuals of European than African ancestry. As a result, the identification of inherited thrombophilia in AAs with otherwise unexplained VTE is much less common than in patients of European descent. Over the past decade, several additional common or low-frequency genetic variants have been discovered through genome-wide association studies (GWASs) or candidate gene resequencing studies of VTE cases and controls.<sup>5</sup> These studies have been conducted largely in individuals of European ancestry, thereby perpetuating the “disparity” in knowledge of genetic determinants of VTE susceptibility among AAs.

In this respect, the GWAS of VTE risk conducted in AAs by Hernandez et al, with the identification of genetic variants located near a biologically plausible gene (*THBD*) associated with VTE risk has potentially important implications. Thrombomodulin is an integral membrane type 1 glycoprotein expressed at high levels on the luminal surface of vascular endothelial cells. Because of its known anticoagulant and antifibrinolytic activities as

a cofactor for thrombin-dependent activation of both protein C and thrombin-activatable fibrinolysis inhibitor (respectively), reduced endothelial thrombomodulin expression could potentially predispose to thrombosis. This hypothesis has been tested in several older studies in European ancestry populations without any definite conclusions.<sup>6,7</sup> Paradoxically, a 1611C>A mutation in the *THBD* gene encodes for a premature stop codon (p.Cys537Stop). Affected individuals shed high levels of soluble thrombomodulin, a potent anticoagulant that leads to a bleeding diathesis.<sup>8</sup> Arguably, however, the most convincing data linking mutations in the *THBD* gene to disease manifestations have been in atypical hemolytic uremic syndrome, as a result of yet another function of thrombomodulin; namely, as a regulator of complement factor I-mediated inactivation of C3b.<sup>9</sup> Therefore, because of the “multitasking” nature of thrombomodulin as a regulatory protein, it is important that any candidate thrombophilic mutations in the *THBD* gene be correlated not only with endothelial cellular expression, but also levels of circulating soluble thrombomodulin and activated protein C, and net plasma thrombin generation potential.

Because the putative *THBD*-related regulatory genetic variants were ~3 times more common among populations of African descent compared with European populations,<sup>1</sup> these loci may contribute to inter-ethnic differences in VTE risk. Thus, confirmation of this finding in prospective cohort studies that include larger numbers of AAs with incidental VTE are critical. Also, because the susceptibility alleles are also present in whites (8% allele frequency), it will be important to assess the “generalizability” of this novel genetic

VTE risk factor not only to Europeans, but also to other ethnic groups such as Hispanics who have both African and European ancestry.

This study highlights the need to conduct genetic association studies of thrombotic outcomes in race/ethnic groups that are most burdened by the disease. Other genetic variation outside the well-established susceptibility loci identified in European studies may contribute to VTE risk in populations of African ancestry. Genetic association studies of quantitative intermediate traits or “endo-phenotypes” for VTE (such as D-dimer, factor VIII levels, or thrombin-generation potential) in large samples of under-represented minority populations may also lead to the identification of additional genetic risk factors for VTE. The use of next-generation sequencing technologies (whole exome or whole genome sequencing) may uncover additional rare variants specific to African populations, which may help to explain disparities in VTE risk.<sup>10</sup> Equally intriguing will be the result of similar studies conducted in Asian American populations, where the risk of VTE appears to be significantly lower than in European and AA cohorts.<sup>2</sup> The recognition of genetic traits that protect against VTE may also lead to exploitable strategies for VTE prevention. As we enter the era of “Precision Medicine,” the knowledge of VTE susceptibility alleles in individuals of African ancestry may ultimately provide important information to improve clinical care and reduce the high burden of disease in this population group.

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